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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, ALEXANDER D	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,338	COSME ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *14-17 and 19-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :09/05/2006, 07/26/2006; 01/27/2006, 06/28/2005, 03/15/2005, 11/30/2004.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on 09/07/2006), Applicants filed a response received on 11/07/2006. Claims 1-20 are pending in this instant Office action.

Election

2. Applicant's election of Group I, Claims 1-13 and 18, is acknowledged. Because applicant did not distinctly and specifically point out the status of traverse in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)). The requirement is therefore made FINAL.
Claims 14-17 and 19-20 are withdrawn from consideration as non-elected inventions.
Claims 1-13 and 18 will be examined herein.

Priority

3. The instant application is a 371 filing of the International Application No. PCT/GB02/02668 filed on 05/30/2002. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Information Disclosure Statement

4. The information disclosure statements (IDSs) filed on 11/30/2004, 03/15/2005, 06/28/2005, 01/27/2006, 07/26/2006 and 09/05/2006 have been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The SEQ. ID NOs are missing for two polypeptide sequences in Claim 11.

Figure 1 teaches amino acid sequences. Labeling using a SEQ ID NO must be inserted into the brief description of the drawings or into the Figure directly.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no

new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID No.

Objections to the Specification

The specification is objected to because of the following informalities:

a. The specification is objected to because the title is not descriptive of the claims. A new title is required that is clearly indicative of the invention to which the claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:

---Methods of purification of cytochrome p450 and their crystallization---

b. The Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the name of the enzyme (cytochrome P450 2D6) and the source species (human) for completeness.

c. The specification has a typographical error in the Table 1, page 30. The "nmoles of 2C19" should be --- nmoles of 2C9 ---. Appropriate correction is required.

Claim Objections

6. Claim 18 is objected to because of the following informalities: Claim 18 recites "analysing" should be ---analyzing---. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-13 and 18 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 (claims 2-13 and 18 dependent therefrom) recite the limitation of position "high-salt lysate" and "high-salt-detergent", which are relative terms. The recited terms used in the claim to describe a certain concentration of salt and/or detergent is unclear without the point of reference. Clarification is required.

8. Claims 4-5 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 (claim 5 dependent therefrom) recites the limitation of "high-salt-detergent" and "high-salt-detergent buffer", which are relative terms. The recited terms used in the claim to describe a certain concentration of salt and/or detergent is unclear without the point of reference. Clarification is required.

9. Claims 4-5 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 (claim 5 dependent therefrom) recite the limitation of position "rapidly desalting", which are relative terms. The recited term "rapidly desalting" used in the claim to describe how fast the desalting has to occur. However, it is unclear how fast is consider a rapid desalting without the point of reference. Clarification is required.

10. Claims 10-12 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 (Claims 11-12 dependent therefrom) recites the limitation "N-terminal membrane inserting element". There is insufficient antecedent basis for this limitation in the claim because its independent Claim 1 is not required to have such an element. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 10-11 are rejected under 35 U.S.C. § 112, first paragraph, written description as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. The instant claims are drawn to a method for purifying cytochrome P450s with certain N-terminal deletions.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed

methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

The instant specification teaches a method for the purification of P450 comprising a deletion in its N-terminal membrane inserting element in Claim 10 (Claim 11 dependent therefrom) wherein the instant specification does not define an "N-terminal membrane inserting element". However, the breadth of the claim includes a method of purifying a P450 having any deletion(s) in the N-terminal. The prior art teaches a method for purifying P450 with N-terminal deletion(s) within the first 22 amino acids of its sequence as disclosed by Wachenfeldt et al. (1997, Archives of Biochemistry and Biophysics, vol. 339, p. 107-114, as cited in the IDS). It is noted that Wachenfeldt et al. do not have the instant purification method steps in correct order as disclosed in Claim 1. The specification discloses a method for purifying a P450 with N-terminal deletion(s) as shown in P450 of SEQ ID NO: 2, 4, 6 or 8. The prior art and the instant specification do not describe a genus method of purifying any N-terminal deleted P450 wherein the N-terminal is membrane inserting element comprising unlimited amino acid residues. A method of instant specification and prior arts do not describe said genus method sufficiently to represent the correlation between the structure and function of claimed genus that is a method of purifying a P450 with any deletion(s) from the N-terminus. Thus, the instant specification and the prior art cannot describe the structure of a very broad claimed genus and one skilled in the art would not be in possession of the claimed genus of the instant specification.

12. Claims 13 and 18 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to a method comprising crystallizing and/or determining the three-dimensional crystal structure of a cytochrome P450.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

Instant specification describes a method of crystallizing cytochrome P450 2C9 (p. 36), co-crystallization of P450 2C19 (p. 40), crystallization of 2C19-1B (p. 43), crystallization of P450 2D6 (p. 54) and crystallization of P450 3A4 (p. 60) in examples. However, the specification does not disclose a description of any other P450 crystallization methods that fall within the instant genera of crystallization methods that includes making a crystal of any P450 protein having any space group symmetry, any unit cell dimensions (including error), and any resolution by any method of crystallization. A genus of method crystallizing any P450, as disclosed in Claims cannot be adequately described by the disclosure of the instant specification. The species of instant case do not correlate structure and function from species to genus. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, any method of crystallization encompassed by the breadth of the claims is not adequately described by the representative species of methods of crystallization disclosed in the

specification. In general, for a species of crystallization method to be adequately described, the following must be disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations, pH and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably, with a SEQ ID NO of all included residues) (2) any ligand added (3) the exact contents of precipitant solution. The species of crystallization noted in Examples of the instant specification, as described above, has adequately met this burden. However, description of this single species fails to adequately describe the genus of crystallization methods encompassed by the breadth of the claims.

A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction [Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: p. 339-350]. Therefore, the suitable crystallization condition(s) disclosed in the specification cannot sufficiently describe a very broad crystallization method, which encompasses any conditions for crystallizing any P450, and one skilled in the art would not be in possession of the claimed genus crystallization methods.

13. Claims 10-11 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method for purifying a P450, i.e., SEQ ID NO: 2, 4, 6, or 8, does not reasonably provide enablement for a

method for purifying a P450 having any deletion(s) from its N-terminus. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use of the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The nature of the invention is drawn to a method for purifying cytochrome P450s with certain N-terminal deletions as shown in instant SEQ ID NO: 2, 4, 6 or 8 compared

to their unmodified amino acid sequences. However, the breadth of claims includes a method for purifying any cytochrome P450 having unlimited deletion(s) from its N-terminus, including deletion of its N-terminal membrane inserting element. Applicants teach a method for purifying four P450 polypeptides in the instant examples and the prior art by Wachenfeldt et al. who disclose purification of P450 2C3 and 2C3H (see Purification on left column, p. 109 and the Table 1 on page 110 of P450 with a certain deletion(s) within the 22nd amino acid from its N-terminus). However, applicants disclose no direction or guidance regarding purification of a P450 with any N-terminal deletion(s) comprising the sequence of MAKKTSSKGR or MAYGTHSHGLFKK. Polypeptide purification methods are dependent on the structure or volume of the polypeptide and a skilled artison would recognize the high level of unpredictability of deleting any N-terminal portion including a membrane inserting element with an expectation of maintaining the ability to purify a protein under given conditions. The large portion of N-terminal deletion would affect the purification method disclosed in the Claim 1. Thus, the specification and prior art fail to describe how to make and use the claimed genus sufficiently. Therefore, it is unpredictable for any N-terminal deleted P450 to be purified in the method of instant disclosure. For all of the above reasons, it would require a large amount of experiment for skilled in the art, thus, undue experimentation is necessary for a method for purifying a P450 with any N-terminal deletion(s).

14. Claims 13 and 18 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method of crystallizing cytochrome P450 2C19 wild type (SEQ ID NO: 2) having speace group of P321, cell dimensions of a=158 Å, b=158 Å, c=212 Å and α=90°, β=90°, γ=120° (see specification p. 40), and P450 3A4 (SEQ ID NO: 8) having the space group C2 and the unit cell dimensions a=152 Å, b=101 Å, c=78 Å and α=90°, β=120°, γ=90° (see specification p. 62), does not reasonably provide enablement for all cytochrome P450 methods of crystal preparation as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* as described above.

The breadth of the claims: Claims 13 and 18 are so broad as to encompass a method that comprises making any cytochrome P450 protein crystals in any crystallization condition and/or determining crystal structure of any cytochrome P450 optionally comprising any ligand by X-ray crystallography. The method excludes a said human 2C9 P450 only under salt buffer concentration is 200 to 1000 mM. Method claims of 13 and 18 are also so broad as to encompass any crystallization method encompassing any cytochrome P450 as described above.

The nature of the invention: The invention is drawn to a method that comprises crystallization of cytochrome P450 2C9, P450 2C19 and co-crystal (p. 40), P450 2C19-

1B, P450 2D6, and P450 3A4 and methods of determining structure coordinate of said protein crystals for a three-dimensional structure determination. At the time of the invention, methods of protein crystallization were well known in the art. However, the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: Regarding the claimed crystals and methods thereof, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed method of crystallization. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al. ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One

cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, *Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 374, bottom). Along these same lines, Wiencek (1999, *Ann Rev Biomed Eng* 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of any cytochrome P450 protein having any sequence can be achieved using the crystallization parameters as set forth in the instant specification. Alternatively, a skilled artisan would recognize that it is highly unpredictable for a method encompassed by the claims as to whether diffraction-quality crystals of any cytochrome P450 protein having any amino acid sequence can be achieved using any crystallization parameters.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only two working examples of crystallizations, and the method of crystallization thereof. Other than these working example(s), the specification fails to provide guidance for altering the crystallization conditions for crystallizing any cytochrome P450 proteins comprising any amino acid sequence with an expectation of obtaining diffraction-quality crystals. Alternatively, the specification fails to indicate whether the disclosed crystallization condition can be applied to any other P450 with an expectation of achieving a diffraction quality crystal. Further, the specification fails to provide guidance for crystallizing a P450 with any P450 binding ligand(s) or any other conditions with an expectation of obtaining diffraction-quality crystals. The instant disclosure has two crystals, i.e., P450 2C19 wild type (SEQ ID NO: 2) and P450 3A4 (SEQ ID NO: 8), that have diffraction quality for a structural analysis. It is unclear if all other crystals would be suitable for structural determination and analysis by the instant specification.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a single protein. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions can be applied to the crystallization of any other cytochrome P450 proteins optionally bound with any ligand under unlimited different sets of crystallization parameters. In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of

unpredictability as evidenced by the prior art, and the amount of experimentation required to crystallize any P450 as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of crystallization condition of any P450 protein and having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4, 6-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by the reference of Kempf et al. (1995, Archives of Biochemistry and Biophysics, vol. 321, p. 277-288, as cited in the IDS) as evidenced by Sigma catalog (H7637 HEPES

hemisodium salt) and Calibiochem catalog (Calbiochem 205534). In the instant case, Claim 1 is drawn to a method for the purification of a cytochrome P450 comprising: expressing in a host cell, recovering the cell from the culture and suspending in a salt buffer having 12 to 110 mS/cm, lysing the cell and removing cell debris, adding a detergent to the lysate, and recovering the P450 from the lysate, wherein the P450 is not a human 2C9 P450 with Pro220 substitution when the salt concentration is 200 to 1000 mM. Claims 2-4, 6-8, and 10 have additional limitations as disclosed in instant claims.

Kempf et al. teach a method for a purification of His-tagged "N-terminal truncated human cytochrome P450 2D6" ([His]$_6$-CYP2D6-Δ25, see bottom of left column, p. 278) and the [His]$_6$-CYP2D6-Δ25 protein as shown in SDS-PAGE gel Figure 3, p. 282, wherein the "N-terminus 25 amino acids --- serve as a membrane anchor" (see Abstract). Kempf et al. teach a method of "transformation into E. coli JM109" with "expression plasmid [His]$_6$-CYP2D6-Δ25" (see top of left column, p. 279). Kempf et al. teach a method of culturing the transformed E. coli as disclosed in "Expression of truncated human P450 2D6" and harvesting "by centrifugation" (see middle of left column, p. 279). Kempf et al. teach a method of resuspending in "buffer AD (150 mM NaCl, --- 50 mM Hepes ---)" (see middle of right column, p. 279). According to the instant specification page 20, "the buffer comprising a salt which is readily soluble to provide a buffer having a conductivity of from 12 to 110 mS/cm" is "desirably a salt having a concentration in the 200-1000 mM range", "preferably the salt is a potassium or sodium salt of an anion" and "Potassium phosphate (KPi) is particularly preferred"

(see page 20, Salt Buffer). Thus, the buffer AD of Kempf et al. have total of 200 mM salt from NaCl and NaHEPES (see HEPES from copy of Sigma catalog in the attachment) and would have conductivity within the range of 12 to 110 mS/cm. The cell of Kempf et al. were lysed by "two passages in a French press", followed by centrifugation (see middle of right column, p. 279) to create a "high-salt lysate" (Claim 1 part c). The "C12E9 --- was added dropwise to a final concentration of 0.2%" (see middle of right column, p. 279), which is a detergent (see Calbiochem: 205534). Kempf et al. teach purification of $[His]_6$-CYP2D6-Δ25 by using Ni^{2+}-NTA-agarose column. The $[His]_6$-2D6-Δ25 bound to the affinity column was "washed with 10 column volumes of buffer AD/0.15% C12E9/0.8 mM imidazole" and "eluted with 10 volumes of buffer AD/0.15% C12E9/40mM imidazole" and followed buffer AD/0.15% C12E9/80 mM imidazole (see middle of right column, p. 279). Kempf et al. teach the pooled fraction was "finally dialyzed with "several changes of 5 mM Hepes buffer" (see bottom of right column, p. 279). Thus, the method of Kempf et al. meets the limitation of Claims 1-4, 6-8 and 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kempf et al. (1995, Archives of Biochemistry and Biophysics, vol. 321, p. 277-288, as cited in the IDS) in view of Anderson et al. (1968, Journal of Bacteriology, vol. 96, p 93-97).

Kempf et al. teach as described above.

Kempf et al. do not teach a method of purification of P450 comprising a step performing a size-exclusion chromatography to remove salt.

Anderson et al. teach a method of isolating an enzyme using "gel filtration served simultaneously to desalt and fractionate the product" (see bottom of left column, p. 94).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice the method of Kempf et al. purifying N-terminal truncated human P450 2D6 and desalting the purified by using a method step performing size-exclusion chromatography of Anderson et al. instead of dialysis with a reasonable expectation of success to desalt P450 2D6 of Kempf et al. because size-exclusion column separates molecules by the size for the same purpose of dialysis by Kempf et al. The motivation to do so is provided by Anderson et al. who disclose "Gel filtration served simultaneously to desalt and fractionate the product" (see bottom of left column, p. 94). Thus, the gel filtration of Anderson et al. would be advantageous for the purification of a protein over the dialysis of Kempf et al. because, in addition to desalting the protein, gel filtration would provide simultaneous additional purification step. Therefore, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/221,036. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims of the instant application and the co-pending application are drawn to a method for the purification of a cytochrome P450 with only one difference, i.e., the claims of the instant application exclude purification of a human 2C9 P450 having position 220 substituted by Pro, whereas the claims in 10/221,036 include all cytochrome P450s.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
January 23, 2007

DAVID J. STEADMAN, PH.D
PRIMARY EXAMINER

Notice to Comply	Application No.	Applicant(s)	
	10/516,338	COSME ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See next page.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510 or (571) 272-2533
For CRF Submission Help, call (571) 272-2510 or (571) 272-2533
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7. cont.

In Claim 11, two polypeptide require SEQ ID NOs.

Figure 1 teaches amino acid sequences. Labeling using a SEQ ID No. must be inserted into the brief description of the drawings or into the Figure directly.